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1- chloroethyl chloroformate debenzylation

1-chloroethyl chloroformate debenzylation. 1-chloroethyl chloroformate density. 1-chloroethyl chloroformate mechanism. 1-chloroethyl chloroformate debenzylation mechanism. 1-chloroethyl chloroformate. 1-chloroethyl chloroformate cas no.

La présente invention concerne un nouveau procédé pour déalkyler des amines tertiaires en utilisant des chloroformiates a-chlorés. Cette invention répond à une question très importante dans le domaine de la synthèse chimique et de la synthèse pharmaceutique, en particulier concernant les amines de base qui nécessitent au moins une substitution pour posséder l'activité optimale. Il s'agit de modifier une amine tertiaire en ajoutant un substituant sans modifier le reste de la molécule. Le principe général consiste à retirer le substituant non désiré par une réaction de déalkylation et à faire réagir l'amine secondaire obtenue avec un halogénure d'alkyle ou un réactif d'alkylation pour obtention de l'amine tertiaire portant le substituent recherché. Ceci est particulièrement important dans le domaine de la synthèse pharmaceutique, où les amines tertiaires sont utilisées en grande quantité, notamment dans la série morphinique. Les produits naturels contenant des amines nécessitent une substitution pour atteindre l'activité optimale, et cette substitution peut se faire uniquement à travers une déalkylation préalable. Currently, there are two primary methods for dealkylating tertiary amines. The first method involves using cyanogen bromide or ethyl and benzyl chloroformates as dealkylating agents, as described in US patents 3254088, 3493657, 3299072, and 3390179. This process reacts the bromide or chloroformate with the amine to be dealkylated, followed by treatment with hydrochloric acid to produce the dealkylated secondary amine. However, this first method has several major drawbacks: it lacks selectivity in eliminating the desired radical and does not provide good yields. Moreover, it requires severe and dangerous reaction conditions, particularly when using cyanogen bromide. The second method, described in US patents 3095981 and 4141897, uses vinyl chloroformate according to the following reaction scheme: This process allows for the dealkylation of tertiary amines but has the drawback of requiring treatment with hydrochloric acid. The acid can attack other substituents on the nitrogen atom, degrading or modifying the molecule, resulting in reduced yields and the need for purification of the dealkylated amine. The present invention aims to propose a dealkylation process that does not have these drawbacks and particularly avoids the risks of degradation of the amine by hydrochloric acid attack. The invention consists of a dealkylation process for a tertiary amine bearing at least one alkyl radical... radical alkyle est la formule dans laquelle R et R2 representent des restes aliphatiques ou cycloaliphatiques, saturés ou non saturés, substitués ou non substitués, des restes aromatiques substitués ou non substitués, les radicaux R1 et R2 peuvent être chimiquement liés l'un à l'autre de manière à former un cycle substitué ou non substitué, R3 représente un reste aliphatique, caractérisé en ce que l'on fait réagir sur l'amine un chloroformiate a-chloré de formule dans laquelle R4 représente un reste aliphatique saturé, substitué ou non substitué par des atomes d'halogènes. Le traitement du carbamate α-chloré avec un solvant hydroxylé léger provoque la coupure du carbamate selon le schéma réactionnel suivant. On récupère ainsi le chlorhydrate de l'amine déalkylée à partir duquel on peut aisément isoler l'amine déalkylée qui n'a subi aucune dégradation d'ordre chimique. Le procédé selon l'invention permet ainsi, par l'emploi de chloroformiates a-chlorés, l'obtention directe, par une simple réaction de condensation, de carbamates α-chlorés à partir desquels il est aisé d'isoler le chlorhydrate de l'amine déalkylée. The procedure involves reacting an alpha-chlorinated carbamate with a tertiary amine, resulting in a hydrochloride that can be easily isolated without compromising other substituents. Unlike traditional methods, this process does not require treatment with hydrochloric acid, reducing the risk of degradation. This method allows for the direct production of high-quality hydrochlorides from dealkylated amines, making it possible to utilize either the hydrochloride or amine without extensive purification. The details of implementing this procedure are as follows: The process initially involves the reaction between an alpha-chlorinated chloroformate and a tertiary amine intended for dealkylation. This method is applicable to most known tertiary amines containing at least one aliphatic radical. The remainder of the molecule outside the aliphatic radical can be composed of two distinct radicals or a saturated or unsaturated, substituted or unsubstituted aliphatic ring optionally containing at least one heteroatom in the ring. If the remainder of the molecule consists of two distinct radicals, these may be identical or different aliphatic or cycloaliphatic residues that are saturated or unsaturated and substituted or unsubstituted. Alternatively, they can be aromatic residues that are substituted or unsubstituted. Examples of tertiary amines fitting this description include: - Aliphatic amines like trimethylamine and triethylamine - Cycloaliphatic amines such as N-methylpiperidine, N-ethylpiperidine, tropine, and N-methylmorpholine - Aromatic amines including N,N-dimethylaniline and N,N-diethyl aniline - Alkaloids like morphine, codeine, alpha-cocaine, beta-cocaine, thebaïne, and N-alkyl acyloxy-14 morphinanes with or without alkoxy or acyloxy groups in position 3 and substituents in position 6. Amines with various functional groups, such as N-methylpiperidine and aromatic amines, are reacting with a-chlorinated chloroformates to form new compounds. The chloroformiates a-chlorés have different R groups, which can be distinct or linked together, and contain between 1 to 30 carbon atoms if they are separate, and 4 to 40 carbon atoms if they are connected. A preferred chloroformiate according to the invention is 1-chloroethyl chloroformate, where the R group is a methyl group. This compound is easily obtained by condensing phosgene on acetaldehyde in the presence of a catalyst. The reaction between the chloroformiate and the tertiary amine occurs at high temperature and usually under anhydrous conditions, with or without solvents. The hydrocarbures halogénés such as dichloro-1,2 éthane or dichloro methane are generally used as solvents, but other solvents like tétrachlorure de carbone, tétrahydrofuranne or toluène can also be employed. However, the demanderesse advises against using these solvants due to the formation of gênant composés during condensation. La transformation totale d'une amine en carbamate est effectuée en présence d'un chloroformiate a-chloré dans des conditions de température élevée. Le choix du solvent est crucial, il doit être inert avec respect à les réactifs introduits et avoir une température d'ébullition relativement élevée. Il est recommandé d'utiliser un solvent anhydre pour éviter toute décomposition du chloroformiate. La durée de réaction varie selon le nombre de radical alkyle présents dans l'amine à déalkyler, avec une transformation totale obtenue en quelques heures. The chloroformate a-chloré is preferably used in excess compared to the normal stoichiometry of the reaction, which can lead to replacing the inert solvent with the chloroformiate a-chloré itself. This results in an easier separation of the products and a significant improvement in yield, especially when the yield is relatively low. A temperature range of 35-150 °C allows for various situations, considering that using high temperatures may be more beneficial if the amine to be dealkylated is expensive. The chlorinated chloroformates degrade into gem-dichlorinated derivatives like dichloro-1,1 ethane and CO2, which are harmless. In contrast, vinyl chloroformates can lead to tarry residues (ill-defined polymers) that are difficult to remove. Once the reaction is complete, the mixture is left to return to ambient temperature, and a light hydroxylated solvent is added in the necessary amount. Preferred alcohols for achieving an effective separation of the carbamate a-chloré include those with 1-4 carbon atoms. The preferred light hydroxylated solvents according to the invention are methanol, ethanol, and water, which yield the best results. The reaction mixture is then agitated and heated to a temperature slightly above ambient temperature, preferably between 35 and 40 °C. After agitation for a duration of 30 minutes to one hour, Le processus selon l'invention permet la déalkylation efficace des amines tertiaires et même des amines avec un cycle aromatique. La méthode consiste à mélanger l'amine avec le chloroformiate a-chloré dans une solution hydroxylée, puis à réduire progressivement la température jusqu'à atteindre une valeur légèrement supérieure à celle de la pièce et d'y maintenir la mixture pendant un temps déterminé. La cleavage totale du chloroformiate a-chloré est garantie par l'ajout d'un solvant hydroxylé comme le méthanol ou l'éthanol, ce qui favorise également une efficace séparation du chlorhydrate d'ammonium déalkylée. La mise en œuvre de la procédure selon l'invention consiste à introduire progressivement le chloroformiate a-chloré dans un réacteur équipé d'un agitateur et d'un réfrigérant, tout en surveillant la température et les taux de conversion des composants. La solution hydroxylée est ensuite ajoutée pour favoriser l'élimination du chloroformiate a-chloré et permettre la récupération de l'ammonium déalkylé sous forme de son chlorhydrate. A reaction mixture was prepared by combining 10.12g of chloro-1-ethyl chloroformate and 50cm3 of anhydrous 1,2-dichloroethane in a 250ml reactor equipped with a mechanical stirrer, thermometer, ascending cooler, and dropping funnel. The apparatus was purged with nitrogen before adding the reagents. Next, 8g of N-ethyl piperidine dissolved in 10cm3 of anhydrous 1,2-dichloroethane was added slowly to the reaction mixture over a period of approximately 15 minutes, while maintaining the temperature between -5 and 0°C. The addition was complete when the reaction mixture was brought to reflux temperature (83°C) and stirred for 1 hour. The reaction mixture was then allowed to return to room temperature and rapidly added with 40cm3 of methanol. The mixture was stirred for an additional 45 minutes at a temperature of 30-35°C before the solvent was removed by evaporation under reduced pressure. As a result, 8.5g of piperidine hydrochloride was obtained, yielding 98.8%. The product had a melting point of 246°C and did not exhibit any impurities in its NMR spectrum. This yield is significantly higher than those reported in Example 1 of US Patent No. 3,905,981, which used different chloroformates. The same procedure was then applied to demethylate N-methyl piperidine: In a 250ml reactor equipped with a mechanical stirrer, thermometer, ascending cooler, and dropping funnel, the apparatus was purged with nitrogen before adding 10.01g of α-chloro ethyl chloroformate and 50ml of anhydrous 1,2-dichloroethane. Next, 6.93g of N-methyl piperidine freshly distilled and dissolved in 10ml of anhydrous 1,2-dichloroethane was added slowly to the reaction mixture over a period of approximately 15 minutes, while maintaining the temperature between -5 and 0°C. The addition was complete when the reaction mixture was brought to reflux temperature (83°C) and stirred for 1 hour. The remaining steps were identical to those described above. The reaction of N-methyl piperidine with α-chloroethyl chloroformate under reflux in dichloroethane yields piperidine hydrochloride with a high yield (97.6%). The synthesis involves dissolving N-methyl piperidine and α-chloroethyl chloroformate in anhydrous dichloroethane, then heating the mixture to around 35-40°C for 45 minutes while stirring. After cooling, methanol is added rapidly, followed by evaporation under reduced pressure to remove the solvent. The resulting piperidine hydrochloride is washed with n-hexane and dried in a desiccator under vacuum. The yield of the reaction is higher than reported in Example 2 of US 3,905,981 for a similar product that still requires treatment to eliminate VOCs. Additionally, three other examples are presented: * De-ethylation of triethylamine: Triethylamine is reacted with α-chloroethyl chloroformate under reflux in dichloroethane, yielding diethylamine hydrochloride with an 85% yield. * Debenzylation of N,N dimethyl benzylamine: This reaction involves the use of α-chloroethyl chloroformate and N,N dimethyl benzylamine under similar conditions as Example 1, resulting in a high-yielding product. Overall, these examples demonstrate the efficiency and effectiveness of the reactions described. Example 1: Demethylation of Tropine to Prepare Nortropin Hydrochloride * Mix 20g of α-chloroethyl chloroformate and 50ml of 1,2-dichloroethane * Add 6.5g of tropine (sublimated at 100°C) and stir for 30 hours * Collect the organic phase and wash it with water and dilute hydrochloric acid * Dry the organic phase over magnesium sulfate and add methanol to precipitate nortropin hydrochloride * Filter, wash, and dry the product (7.5g obtained, 78% yield) * Melting point: 283°C (literature value: 285°C) Example 2: Demethylation of N,N-Dimethylaniline * Use the same apparatus as in Example 1 * Mix 10.1g of α-chloroethyl chloroformate and 50ml of anhydrous 1,2-dichloroethane * Add 8.47g of freshly distilled N,N-dimethylaniline over 15 minutes while maintaining the temperature between -5°C to 0°C * Reflux for 30 hours, then cool and wash with water and dilute hydrochloric acid * Dry the organic phase over magnesium sulfate and add methanol to precipitate N-methylaniline hydrochloride * Filter, wash, and dry the product (3.6g obtained, 36% yield) * Melting point: 126°C (literature value: 122-123°C) In summary, two examples of demethylation reactions are described, each using a different starting material (tropine or N,N-dimethylaniline) and resulting in the formation of different products (nortropin hydrochloride or N-methylaniline hydrochloride). A highly pure product can be obtained through a single reaction step. Here's an example: Example 7: Deethylation of N-Ethyl Piperidine with 1-Chloro-Chloro Pentyl Chloroformate The procedure is identical to Example 1, using the following raw materials: * 7.4 g (0.04 mole) of 1-chloro- chloro pentyl chloroformate in 30 ml of dichloro 1-2 ethane * 4.52 g (0.04 mole) of N-Ethyl Piperidine in 10 ml of dichloro 1-2 ethane After treatment with methanol, 4.6 g (94.5%) of piperidine hydrochloride, melting at 244 °C, are obtained. Example 8: This test is identical to Example 7 but the methanol is replaced by the same amount of ethanol. The product is also piperidine hydrochloride, melting at 244 °C, and is obtained in a yield of 99.3%. Example 9: This test is identical to Example 1 but dichloro 1-2 ethane is replaced by methylene chloride. Two hours of heating at reflux are necessary to prepare the a-chlorinated carbamate. From 7.91 g (0.07 mole) of N-Ethyl Piperidine, 8.5 g (100%) of piperidine hydrochloride are obtained. Example 10: This test is identical to Example 9 but methylene chloride is replaced by carbon tetrachloride. The reflux time for the preparation of the a-chlorinated carbamate is 1 hour. The product is piperidine hydrochloride, melting at 244-245 °C, and is obtained in a yield of 97.6%. Example 11: This test is identical to Example 10 but the solvent used is tetrahydrofuran. The product is piperidine hydrochloride, melting at 244-245 °C, and is obtained in a yield of 98.8%. Example 12: This test is identical to Example 10 but the solvent used is toluene. The product is piperidine hydrochloride, melting at 244-245 °C, and is obtained in a yield of 97.6%. Example 13: The demethylation reaction for N-methyl morpholine was conducted using 7.07 g (0.07 mole) of N-methyl morpholine and 10.01 g (0.07 mole) of α-chloroethyl chloroformate, resulting in 8.3 g (96%) of morpholine hydrochloride with a melting point of 174-177 °C. The invention allows for the dealkylation of aromatic amines, which is typically challenging. In a series of experiments, it was found that using α-chlorinated chloroformate as a solvent improves the reaction outcome. In one experiment, an attempt was made to monodeethylate 8-diethylamino-tetrahydro-1,2,3,4-dibenzofuran (DTB) using vinyl chloroformate. However, no reaction occurred even after heating for 48 hours. In another experiment, the same conditions were used, but with α-chloroethyl chloroformate and DTB introduced at -5 °C instead of -35 °C. The reaction was followed by vapor phase chromatography and found to be slow. After 48 hours, a yield of 40% was achieved for monodeethylated amine, which was obtained by treating the reaction mixture with sodium hydroxide and then extracting it with methanol and ether. The reaction mixture was treated with methanol to decompose it, then with sodium hydroxide solution and ether to extract the product. This process resulted in a yield of 40% monodeethylated amine. In a new experiment, the reaction was performed without solvent. The reactants were heated to 130°C for 30 hours, resulting in an improved yield of 83%. The same reaction was repeated with different concentrations of DTB and chloroformate, yielding 89% product. Another variation of the reaction involved replacing DTB with a similar diamine that differed only by one carbon atom. This resulted in a yield of 80% monodeethylated product. A further modification of the reaction involved replacing DTB with another compound and shortening the reaction time to just one hour, yielding 86%. Finally, the reaction was scaled up in a large reactor and performed under conditions that included mechanical stirring and temperature control. The reactants were introduced into the reactor, along with anhydrous dichloroethane, and the mixture was maintained at a temperature between -5°C and 0°C. In a 10 cm³ anhydrous dichloro-1,2 ethane solution maintained at -5 to 0 °C, the reaction mixture was brought to reflux of the solvent (83 °C) for 1 hour and then cooled to room temperature. The solvent was evaporated using a relative evaporator. To the residue, 40 cm³ of THF and 2 cm³ of water were added, and the mixture was stirred at 40 °C for 1.5 hours. Subsequently, 2.5 cm³ of water were added to the mixture, and it was again stirred for 1.5 hours at reflux of THF (66 °C). After these three hours of treatment, only about 50% conversion of carbamate to hydrochloride was achieved. To improve this result, 40 cm³ of methanol were added, and the mixture was stirred for 45 minutes at 40-45 °C. It was found that water enabled the transformation from carbamate to secondary amine hydrochloride, but methanol proved more effective in this process. Better results were obtained when only water (10 cm³) was added after evaporation of dichloro-1,2 ethane and heated between 60 and 80 °C for 1 to 3 hours.